UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/537,543	06/03/2005	Nigel K.H. Slater	BJS-620-366	4805

23117 7590 12/20/2006
NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

EXAMINER	
MAKAR, KIMBERLY A	
ART UNIT	PAPER NUMBER
1636	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/20/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/537,543	SLATER ET AL.	
	Examiner	Art Unit	
	Kimberly A. Makar	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *153-194* is/are pending in the application.

4a) Of the above claim(s) *191-194* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *153-190* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 June 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07/20/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

1. Applicant's election without traverse of group I in the reply filed on 09/25/06 is acknowledged.

2. Claims 191-194 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 09/25/06.

Information Disclosure Statement

3. The information disclosure statement filed 07/20/05 fails to comply with 37 CFR 1.98(a)(1), which requires the following: (1) a list of all patents, publications, applications, or other information submitted for consideration by the Office; (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; (3) the application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information disclosure statement. The information disclosure statement has been placed in the application file, but the information referred to therein has not been considered. A copy of the article by Weissleder et al, 1999 was not provided, and thus not considered.

Specification

4. The disclosure is objected to because of the following informalities: The specification refers to claims. Reference to claim numbers is improper and must be deleted.

5. Appropriate correction is required.

Abstract

6. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

7. The abstract of the disclosure is objected to because the abstract contains the legal phraseology "said payload". Correction is required. See MPEP § 608.01(b).

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 153-190 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

10. The Guidelines for Written Description state "The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art" (Federal Register/ Vol. 66, No. 4/Friday, January 5, 2001/Notices, column 1, page 1105). The Guidelines further state, "[t]he claim as a whole, including all limitations found in the preamble, the transitional phrase, and the body of the claim, must be sufficiently supported to satisfy the written description requirement" (at page 1105, center column, third full paragraph). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations. *Lockwood v. American Airlines Inc.* (CA FC) 41 USPQ2d 1961 (at 1966).

11. Applicants claim 153 (an dependent claims) recites a process for the delivery of a payload into the nucleus of a living cell, comprising contacting the cell with a hypercoiling carrier polymer which incorporated or is associated with the payload, wherein said hypercoiling carrier polymer has both hydrophobic regions and hydrophilic regions. The claim therefore reads on a genus of methods involving *any* previously

known or unidentified hypercoiling carrier polymers associated with *any* payload into *any* living cell.

12. The written description requirement for a genus may be satisfied by sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that applicant was in possession of the claimed invention.

13. In the instant case, applicants have provided no description of a representative number of methods using any hypercoiling carrier polymer with both hydrophobic and hydrophilic regions associated with any payload that has nuclear localization in any living cell. Applicants do provide evidence of a method comprising Poly(L-lysine-co-Cy3-iso-phthalamide) (PD30) as the carrier polymer with the payload Cy3 having nuclear localization in CHO and HepG2 cells (page 111-112, and Figures 21 and 22). This method involved incubation of PD30 with the cells for 24 hours before confocal microscopy images were taken (page 111). However, using the same conditions, the method comprising Poly(L-lysine-co-Cy3-iso-phthalamide) and Cy3 dye (PD20) using identical conditions in HepG2 cells (a 24 hour incubation followed by confocal microscopy), reveals endosomal localization of the Cy3 dye (page 110-111 and Figure 20). Closer inspection of Figure 20 shows a lack of nuclear staining for the PD20 carrier copolymer and Cy3 dye in these cells. Applicants do not disclose any other working

examples of carrier polymers that are capable of nuclear localization other than PD30, although applicants disclose the production of several hypercoiling polymers, and that they show as having the ability to enter the cell (Poly(L-lysine iso-phthalamide) and doxorubicine (page 12) they do no disclose the final localization of the doxorubicine in the nucleus. The specification does not address what is specific about *any* hypercoiling carrier polymer with hydrophobic and hydrophilic regions that is capable of delivering *any* payload to the nucleus of *any* living cell. The skilled artisan would be unable to identify any specific characteristic of *any* hypercoiling carrier polymer that would direct the localization of *any* payload into the nucleus of any cell based on applicants' disclosure. The skilled artisan would therefore conclude that applicants have not provided sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics of methods comprising *any* hypercoiling carrier polymers and *any* payload with nuclear localization capabilities in *any* living cells and therefore were not in possession of the claimed invention. The disclosure of a single species Poly(L-lysine-co-Cy3-iso-phthalamide) and Cy3 (PD30) would therefore not be considered by the skilled artisan to be a representative number of species sufficient to describe the claimed genus.

14. Claims 153-190 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of delivering a Cy3 dye into the nucleus of a living cell, comprising contacting the cell with the hypercoiling carrier copolymer Poly(L-lysine-co-Cy3-iso-phthalamide), does not reasonably provide enablement for a

method of delivering any payload into the nucleus of any living cell, comprising contacting the cell with any hypercoiling carrier polymer which incorporates, or is otherwise associated with, said payload, wherein said hypercoiling carrier polymer has both hydrophobic and hydrophilic regions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or practice the invention commensurate in scope with these claims.

15. The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based on a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter., 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following:

16. 1) The nature of the invention. The invention involves a method of delivering any payload into the nucleus of any living cell, comprising contacting the cell with any hypercoiling carrier polymer which incorporates, or is otherwise associated with, said payload, wherein said hypercoiling carrier polymer has both hydrophobic and hydrophilic regions. This reads on methods comprising thousands of different permutations of hypercoiling polymers with different cell types and different payloads. Claims 169-170,178, and 179 restrict the hypercoiling polymers to nearly an infinite possibility to configurations depending on the different hydrophobic and/or functional

group permutations that could affect the transducability and localization of the polymer complex into and through the cell. Claims 186-188 comprise potentially thousands of compounds with different characteristics that could also affect the transducability and localization of the polymer complex into and through the cell.

17. 2) State of the art. The art shows there are no examples of methods involving a method of delivering any payload into the nucleus of any living cell, comprising contacting the cell with any hypercoiling carrier polymer which incorporates, or is otherwise associated with, said payload, wherein said hypercoiling carrier polymer has both hydrophobic and hydrophilic regions. The art does reveal a method of nuclear localization in HepG2 cells of copolymers comprising the pH-responsive HPMA polymer and a variety of dyes (fluorescein, Oregon Green 488, rhodamine B and doxorubicin) taught by Jensen et al, 2001 (provided in applicant IDS 1449 form dated 7/20/05). HPMA is neutrally charged and not amphipathic. Jensen further reveals that one copolymer, P5, which comprises HPMA and doxorubicin had "less pronounced [nuclear] staining" compared to the other polymers tested which Jensen explains as possible quenching of DOX, but then mentions that DOX has different localization patterns in cells depending upon the type of polymer it is attached to, and what type of cell the DOX enters (pages 12-13). A review of the patent literature reveals several examples of hypercoiling carrier polymers which incorporate, or is otherwise associated with, said payload, wherein said hypercoiling carrier polymer has both hydrophobic and hydrophilic regions and has nuclear localization as a general target for the polymer or due to the specific presence of a nuclear localization signal (see US Patent 5,977,084,

US PG Publication No: US 2003/0026841 and US2005/0154165). Thus there appears to be some known obstacles of nuclear localization patterns of known pH-sensitive polymers and payloads depending upon the type of payload and the cells tested.

18. 3) Unpredictability of the art. The art is highly unpredictable. Due to the highly variable number of alterations of the polymer backbone, sidechains, copolymer configurations, types of payload and variety of cells to transduce, applicants do not disclose how, if the method comprised any amphipathic pH-responsive polymer and any payload in any cell how one would overcome known problems in the art for successful nuclear delivery? Given the range of hundreds of potential amphipathic pH-responsive polymers utilized, hundreds of payloads, and the numerous cell types, one of skill in the art would have to perform trial and error in order to perform the method as claimed in the instant invention.

19. 4) Number of working examples. Applicants do provide evidence of a method comprising Poly(L-lysine-co-Cy3-iso-phthalamide) (PD30) as the carrier polymer with the payload Cy3 having nuclear localization in CHO and HepG2 cells (page 111-112, and Figures 21 and 22). This method involved incubation of PD30 with the cells for 24 hours before confocal microscopy images were taken (page 111). However, using the same conditions, the method comprising Poly(L-lysine-co-Cy3-iso-phthalamide) and Cy3 dye (PD20) using identical conditions in HepG2 cells (a 24 hour incubation followed by confocal microscopy), reveals endosomal localization of the Cy3 dye (page 110-111 and Figure 20). Closer inspection of Figure 20 shows a lack of nuclear staining for the PD20 carrier copolymer and Cy3 dye in these cells. Applicants do not disclose any

other working examples of carrier polymers that are capable of nuclear localization other than PD30, although applicants disclose the production of several hypercoiling polymers, and that they show as having the ability to enter the cell (Poly(L-lysine iso-phthalamide) and doxorubicine (page 12) they do no disclose the final localization of the doxorubicine in the nucleus. The specification does not address what is specific about any hypercoiling carrier polymer with hydrophobic and hydrophilic regions that is capable of delivering any payload to the nucleus of any living cell. Lack of instruction on the method of the large variety of possible permutations of the invention, a skilled artisan would have to perform trial and error in order to practice the claimed invention.

20. 5) Amount of direction or guidance present. The applicants provide specific examples of making a variety of Poly(L-lysine iso-phthalamide) copolymers with dye conjugates, but only provide guidance on the nuclear localization of one polymer capable of actual nuclear localization Poly(L-lysine-co-Cy3-iso-phthalamide) and Cy3 dye (PD30) (page 111-112). Applicants do not teach that the nuclear localization of the polymer is due to the presence of a specific localization signal in the polymer, and that nuclear localization was an unexpected result (page 15 of the instant specification).

21. 6) Level of skill in the art. The level of skill is high. Given that the range of hundreds of potential amphipathic pH-responsive polymers utilized, hundreds of different payloads, combined with the numerous potential cell types, one of skill in the art would have to perform trial and error in order to perform the method as claimed in the instant invention, rendering a high degree of skill in order to practice the claimed invention.

22. 7) The breadth of the claims. The breadth of the claims is broad and involves a method of delivering any payload into the nucleus of any living cell, comprising contacting the cell with any hypercoiling carrier polymer which incorporates, or is otherwise associated with, said payload, wherein said hypercoiling carrier polymer has both hydrophobic and hydrophilic regions. This reads on method comprising thousands of different permutations of hypercoiling polymers with different cell types and different payloads.

23. Given the above analysis of the factors which the courts have determined are critical in ascertaining whether a claimed invention is enabled, including the highly unpredictable art, the scarcity of working examples provided by applicant, the lack of guidance by the applicant, and the broad nature of the invention it must be considered that the skilled artisan would have to conduct undue and excessive experimentation in order to practice the method of the claimed invention.

24. It is noted that this Office Action contains rejections of the same claims under 35 USC 112, 1st (enablement) and 35 USC 102 (e). While these rejections may seem contradictory, they are not because each is based upon a different legal analysis, i.e. sufficiency of the disclosure of the instant application to support claims under 35 USC 112, 1st paragraph vs. sufficiency of a prior art disclosure to anticipate or render obvious an embodiment(s) of the claimed invention (See *In re Hafner*, 161 USPQ 783 (CCPA 1969)).

25. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

26. Claims 169-174, and 179-182 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 169-174, and 179-182 use the phrase "derived from" in reference to different chemical structures. The term "derived from" is not clearly defined in the specification. The specification reads, "Note that the term "derived from," as used herein, indicates that the specified group may be derived from the specified source, and not that it is necessarily derived from the specified source." (page 34 of the instant specification). However, this definition fails to clearly delineate what "derived from" actually means. The phrase "derived from" implies something is changed from a starting source. How much change is required? In terms of chemical structures, how many alterations are made, and what type? Are additional bonds made? Are carbon atoms exchanged for sulfurs? Are certain elements phosphorylated? There is no limit on the phrase "derived from" and thus is unclear. A skilled artisan would be unable to determine the meets and bounds of the invention as claimed.

For the purposes of prosecution, the following terms are defined:

27. "The term "hypercoiling," as used herein, pertains to a polymer which undergoes a hypercoiling transition upon change of pH, for example across a threshold pH." (Page 16 of the instant specification.)

28. "The term "hypercoiling transition," as used herein, pertains to the transition of a polymer from a rod to a globule (e.g., coil, helix), or from a globule (e.g., coil, helix) to a rod." (Page 16 of the instant specification.)

29. "In this respect, the carrier polymer is a "pH responsive polymer," that is, the polymer changes conformation in response to a change in pH, for example across a threshold pH." (Page 16 of the instant specification.)

30. "The term "amphiphilic" (and "amphipathic"), as used herein, pertains to a polymer which has both hydrophobic regions and hydrophilic regions." (Page 26 of the instant specification.)

31. "The term "biodegradable", as used herein, pertains to a polymer which is substantially degraded in vivo, e.g., in (or in contact with) the cells with which it is to be used." (Page 21 of the instant specification.)

32. "The term "biocompatible", as used herein, pertains to a polymer which is substantially non-toxic, that is, substantially non-cytotoxic, e.g., towards the cells with which it is to be used." (Page 21 of the instant specification.)

33. Furthermore, Tonge et al (Responsive hydrophobically associating polymers: a review of structure and properties. Advanced Drug delivery Review, 2001. 53:109-122), provided in applicant IDS 1449 form dated 7/20/05 teaches:

> Responsive hydrophobically associating polymers can in many ways be considered to be analogous to proteins in their ability to form compact molecules with a defined secondary structure, and hence functionality. These molecules are characterized by the presence of alternating charged and hydrophobic groups. (Page 109)
>
> And

Hence, by substituting either weakly cationic or anionic pendant groups onto a polymer backbone, the polymer can be made to respond to either increases or decreases in pH. This mechanism can be made to respond to the pH of their surrounding environment, and possibly behave in a similar manner to the responsive macromolecules found in nature. However, it should be noted that protein molecules do not hypercoil, per se, but are subject to hydrophobic associative forces, although changes in pH may result in the formation of certain secondary structures within protein, such as the α-helix or β-pleated sheet conformations." (page 110)

Thus, using the definitions provided by applicant, a "hypercoiling carrier polymer" is an amphipathic or amphiphilic polymer that responds to pH by a change in conformation. Tonge et al teaches that proteins inherently comprise the ability to change conformation (produce α-helix or β-pleated sheet conformations) in response to pH. Thus any amphipathic or amphiphilic protein fulfills the definition requirements of "hypercoiling carrier polymer" as defined by applicant.

Claim Rejections - 35 USC § 102

34. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

35. Claims 153-156, 159-162, 177-178, 181-182, and 186-190 are rejected under 35 U.S.C. 102(b) as being taught by Szoka et al (US Patent No: 5,977,084). Claims 153-156, 159-162, 177-178, 181-182, and 186-190 recite a method of delivering a payload into the nucleus of a living cell, comprising contacting the cell with a hypercoiling carrier polymer which incorporates, or is otherwise associated with, said payload, wherein said hypercoiling carrier polymer has both hydrophobic regions and hydrophilic regions (claim 153) wherein said payload forms part of the backbone of said hypercoiling carrier polymer (claim 154) and wherein said payload is tethered to the backbone of said hypercoiling carrier polymer (claim 155) and wherein said hypercoiling carrier polymer is associated with said payload, and forms a complex with said payload (claim 156). The method if further limited wherein the carrier polymer is biocompatible (claim 157) and biodegradable (158). The method is further limited wherein the carrier polymer is not a vinyl polymer (claim 159) and wherein the carrier polymer has a backbone having amide linkages (claim 160) a backbone having ester linkages and amide linkages (claim 161).

36. The method is further limited wherein said hypercoiling carrier polymer has both hydrophobic regions and hydrophilic regions, and wherein said hydrophobic regions and hydrophilic regions alternate along the length of the backbone of the carrier polymer (claim 162) and wherein at least one of the hydrophilic moieties bears a carboxylic acid group or a salt thereof (claim 177) and wherein at least one of the hydrophilic moieties bears an amino acid base group selected from a primary amino group (NH_2) (claim 178) and at least one of the hydrophilic moieties are selected from moieties derived from amino acids (claim 181) and wherein at least one of the hydrophilic moieties are

selected from moieties derived from the following compounds: 2,4-diaminopropionic acid; 2,4-diaminobutyric acid; ornithine; lysine; 2,6-diaminopimelic acid (claim 182).

37. The method is further limited wherein one or more of the payload moieties are, or comprise, biologically active agents selected from: (a) drugs, prodrugs, chemo-therapeutics, radio-therapeutics, neutron capture agents; (b) peptides, proteins, antibodies, antibody fragments, enzymes, transcription factors, signaling proteins, antisense peptides, zinc fingers, peptide vaccines; and, (c) nucleotides, oligonucleotides, plasmids, nucleic acids (claim 186) and wherein one or more of the payload moieties are, or comprise, detectable labels selected from: (a) fluorophores; (b) chromophores; (c) isotopically enriched species; (d) paramagnetic species; (e) radioactive species; and, (f) scintillents and phosphors (claim 187) and wherein one or more of the payload moieties is a cyanine dye or a derivative thereof, a chelating group capable of complexing with a detectable label, a drug, or a boron-containing moiety, or one or more of the payload moieties is, or comprises, a peptide, a nucleic acid, or a cationic nucleic acid complex (claim 188).

38. The method is further limited wherein the carrier polymer further comprises other regions and/or moieties selected from: spacer groups, water solubilizing groups, and targeting ligands (claim 189) and wherein the carrier polymer further comprises water solubilizing groups selected from: polyethylene glycol (PEG), poly ethylene oxide (PEO), polyvinyl alcohol (PVA), hydroxylpropylmethyl alcohol (HPMA), and dextran groups (claim 190).

39. Szoka et al (US Patent No: 5,977,084) teaches complexes comprising DNA masking components for the delivery of DNA (ie payload) into cells (see Abstract). Szoka teaches that the DNA masking components comprise amphipathic peptides, and that these peptides contain some or all of the amino acids in the D or L configuration (Column 12, lines 30-39). Szoka teaches that the DNA masking components further comprise "membrane permeabilizers" such as nonvinyl polycations including polylysine, polyarginine, poly(lysine-arginine) as well as polyamines (ie polyamides) (Column 11, lines 60-65). Szoka further teaches that "a membrane permeabilizer may be a peptide, bile salt, glycolipid, carbohydrate, phospholipids or detergent molecule. Membrane permeabilizers often have amphipathic properties such that one portion is hydrophobic and another is hydrophilic, permitting them to interact with membranes" (column 7, lines 56-61). Additionally, Szoka teaches that the lipids are also amphipathic (column 12, lines 44-49) and that the amphipathic phospholipids are pH-sensitive (see example 1). Szoka also teaches that the DNA-peptide complexes can comprise either lipid or polyamines, or both (column 12, lines 41-43).

40. Furthermore, Szoka teaches the polymers comprise amide bonds via the reactive acyl group carboxylic acids in polymers comprising polyamines. Applicants define "peptide linkage" as "an amide linkage which is formed by reaction of a α-amino group of one α-amino acid and an α-carboxylic acid group of another α-amino acid." (page 23 of the instant specification.) Szoka teaches the biocompatible hydrophilic poly amino acid polylysine which inherently has amino acid base groups of primary amino groups (-NH_2) in the DNA masking component.

41. Szoka teaches that "the sugar-phosphate backbone of the polynucleotide may be replaced with a non-carbohydrate backbone, such as a peptide or other type of polymer backbone" (column 7, lines 30-32) thus teaching that the payload forms part of the backbone of the carrier polymer. Szoka further teaches that the carrier polymer can be complexed to the DNA (ie payload) via noncovalent interactions (column 8, lines 23-25) or through covalent linkages (column 8, lines 38-40). The covalent linkages occur through functional reactive groups including amine groups (column 8, lines 44-46).

42. The DNA polymer complexes can be further modified by the addition of cell targeting and recognition components such as antibodies and ligands (column 11, lines 23-25) and the addition of biodegradable linkers (ie spacer groups) such as lysine linkages (column 15, lines 22-24) and the addition of polyethylene glycol groups covalently added to the polymer (column 10, lines 7-14). Additional modifications include that addition of nuclear localization peptides or nuclear localization signals to the DNA polymer complex for targeted nuclear localization of the payload into living cells (column 3, lines 60-67 and Example 7). Szoka teaches that the payload comprises a plasmid polynucleotide that encodes the fluorophore luciferase (see Example 1).

43. Thus Szoka teaches a method comprising pH-responsive amphipathic biocompatible and biodegradable hypercoiling polymers derived from polyamines comprising the hydrophilic amino acid lysine carrier for the nuclear delivery of a payload into a living cell, wherein the hypercoiling polymer comprises hydrophobic and hydrophilic regions, wherein the payload includes nucleotides, peptides, and fluorophores. Furthermore Szoka teaches that the interactions between the payload

and the pH-responsive hypercoiling polymers are noncovalent and covalent, and allow for the payload to comprise part of the backbone of the complex. Thus Szoka teaches the claimed invention.

44. Claims 153, 155-156, 159-162, 177-178, 181-182, and 186-190 are rejected under 35 U.S.C. 102(e) as being taught by Trubetskoy et al (US Patent Publication US 2003/0026841). Claims 153-156, 159-162, 177-178, 181-182, and 186-190 recite a method of delivering a payload into the nucleus of a living cell, comprising contacting the cell with a hypercoiling carrier polymer which incorporates, or is otherwise associated with, said payload, wherein said hypercoiling carrier polymer has both hydrophobic regions and hydrophilic regions (claim 153) and wherein said payload is tethered to the backbone of said hypercoiling carrier polymer (claim 155) and wherein said hypercoiling carrier polymer is associated with said payload, and forms a complex with said payload (claim 156). The method if further limited wherein the carrier polymer is biocompatible (claim 157) and biodegradable (158). The method is further limited wherein the carrier polymer is not a vinyl polymer (claim 159) and wherein the carrier polymer has a backbone having amide linkages (claim 160) a backbone having ester linkages and amide linkages (claim 161).

45. The method is further limited wherein said hypercoiling carrier polymer has both hydrophobic regions and hydrophilic regions, and wherein said hydrophobic regions and hydrophilic regions alternate along the length of the backbone of the carrier polymer (claim 162) and wherein at least one of the hydrophilic moieties bears a carboxylic acid group or a salt thereof (claim 177) and wherein at least one of the hydrophilic moieties

bears an amino acid base group selected from a primary amino group (NH_2) (claim 178) and at least one of the hydrophilic moieties are selected from moieties derived from amino acids (claim 181) and wherein at least one of the hydrophilic moieties are selected from moieties derived from the following compounds: 2,4-diaminopropionic acid; 2,4-diaminobutyric acid; ornithine; lysine; 2,6-diaminopimelic acid (claim 182).

46. The method is further limited wherein one or more of the payload moieties are, or comprise, biologically active agents selected from: (a) drugs, prodrugs, chemo-therapeutics, radio-therapeutics, neutron capture agents; (b) peptides, proteins, antibodies, antibody fragments, enzymes, transcription factors, signaling proteins, antisense peptides, zinc fingers, peptide vaccines; and, (c) nucleotides, oligonucleotides, plasmids, nucleic acids (claim 186) and wherein one or more of the payload moieties are, or comprise, detectable labels selected from: (a) fluorophores; (b) chromophores; (c) isotopically enriched species; (d) paramagnetic species; (e) radioactive species; and, (f) scintillents and phosphors (claim 187) and wherein one or more of the payload moieties is a cyanine dye or a derivative thereof, a chelating group capable of complexing with a detectable label, a drug, or a boron-containing moiety, or one or more of the payload moieties is, or comprises, a peptide, a nucleic acid, or a cationic nucleic acid complex (claim 188).

47. The method is further limited wherein the carrier polymer further comprises other regions and/or moieties selected from: spacer groups, water solubilizing groups, and targeting ligands (claim 189) and wherein the carrier polymer further comprises water solubilizing groups selected from: polyethylene glycol (PEG), poly ethylene oxide

(PEO), polyvinyl alcohol (PVA), hydroxylpropylmethyl alcohol (HPMA), and dextran groups (claim 190).

48. Trubetskoy et al (US Patnt Publication US 2003/0026841) teaches a polyampholyte and polynucleotide complex for cellular delivery (see abstract). Trubetskoy teaches that polyampholytes are "copolyelectrolytes contains both polycations and polyanions in the same polymer." (page 5, paragraph 0051). He teaches alternating copolyampholytes, which are "polyampholytes in which the cationic and anionic monomers repeat in a repeating alternating sequence. The monomers in these polyampholytes may, but need not be, polymers themselves." (page 6, paragraph 0058). Examples of cationic polymers used in the invention are poly-L-lysine and polyethylenimine (page 6, paragraph 0060). Trubetskoy teaches the incorporation of amphiphilic and amphipathic compounds, which have both hydrophobic and hydrophobic regions (page 11, paragraph 0140). He teaches, "[e]xamples of hydrophilic groups include compounds with the following chemical moieties; carbohydrates, polyoxyethlyene, peptides, oligonucleotides and groups containing amines, amides, alkoxy amides, carboxylic acids, sulfurs, or hydroxyls." (page 11, paragraph 0140). Trubetskoy teaches that polymers can be a copolymer in which two or more monomers are used resulting an alternating pattern (page 12, paragraphs 0151- 0155). He further teaches that monomers are hydrophobic, hydrophilic or amphipathic (page 13, paragraph 0169), thus teaching a polymer comprising alternating copolymer comprising alternating hydrophobic and hydrophilic regions.

49. Trubetskoy teaches functional groups and reaction of "amines, hydroxyl, thiol, sulfhydryl, caroxylate groups which yield chemical bonds that are described as amide, amidine, disulfide, ethers, esters, enamine, urea, isothiourea, isourea, sulfonamide, carbamate, carbon-nitrogen double bond (imine), alkylamine bond (secondary amine), carbon-nitrogen single bonds in which the carbon contains a hydroxyl group, thio-ether, diol, hydrazone, diazo, or sulfone" (page 13, lines 0165). He teaches that the amines are pH-sensitive (page 13, paragraph 0168).

50. Trubetskoy teaches the complexes further comprise polyethylene glycol (PEG) stabilizing groups (page 14, paragraph 0180). Trubetskoy teaches nonvinyl polymers comprising hydrophilic polylysine (page 12, paragraph 0152), polyoxyethylene (page 15, paragraph 0221) as well as a variety of polycations and polyanions (page 19, paragraph 0281-0282). Trubetskoy teaches the compounds include the activation of a carboxylate, which is a carboxylic acid derivative that reacts with nucleophiles to form a new covalent bond. Nucleophiles include nitrogen, oxygen, and sulfur compounds to produce ureas, amides, carbonates, carbamates, esters, and thioesters (page 16, paragraph 0231).

51. Trubetskoy teaches that the compounds further comprise biodegradable pH-labile bonds (page 16, 0250 – 0254) which can be part of the main chain of the side chain of the polymers. Additionally linkers, or spacer molecules, are used to conjugate passenger molecules and carrier (ie pH-responsive polymers) molecules (page 17, paragraph 0260). Carrier molecules include biologically active compounds, such as "pharmaceuticals, proteins, peptides, polypeptides, enzyme inhibitors, hormones,

cytokines, antigens, viruses, oligonucleotides, enzymes, and nucleic acids" (page 7, paragraph 0073). Additional modifications include the addition of reporter or marker molecules, such as "fluorescein, rhodamine, Texas red, cy5, cy3 or dansyl compounds" (page 11, paragraph 0124). Trubetskoy teaches the compounds comprise both noncovalent and covalent bonds (page 14, paragraph 0187).

52. Additionally, Trubetskoy teaches that the carrier and payload complexes can be targeted to the nucleus via nuclear localization signals in a peptide or nucleic acid (page 10, paragraph 0118). Trubetskoy further teaches that the compounds are nontoxic (page 6, paragraph 0063), thus biodegrable and biocompatible.

53. Thus Trubetskoy teaches a method comprising pH-responsive amphipathic biocompatible and biodegradable hypercoiling polymers derived from polyamines comprising the hydrophilic amino acid lysine carrier for the nuclear delivery of a payload into a living cell, wherein the hypercoiling polymer comprises hydrophobic and hydrophilic regions, wherein the payload includes nucleotides, peptides, and fluorophores. Furthermore Trubetskoy teaches that the interactions between the payload and the pH-responsive hypercoiling polymers are noncovalent and covalent. Thus Trubetskoy teaches the claimed invention.

Conclusion

54. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Makar, Ph.D. whose telephone number is 571-272-4139. The examiner can normally be reached on 8AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

kam/12/10/06

DAVID GUZO
PRIMARY EXAMINER